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Two installments 1 of 34

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MESSAGE:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Donald L. Wise, Debra J. Trantolo, David D. Hile, and Stephen A. Doherty

Serial No.: 10/613,975 Art Unit: 1645

Filed: July 3, 2003 Examiner: Khatol Shahnan-Shah

For: *VACCINES TO INDUCE MUCOSAL IMMUNITY*

Attachments:
Transmittal Form PTO/SB/21;
Fee Transmittal Form PTO/SB/17;
Appeal Brief; and
Ten (10) References

PTO/SB/21 (09-04)
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Application Number	10/613,974
Filing Date	July 3, 2003
First Named Inventor	Donald L. Wise
Art Unit	1645
Examiner Name	Khatol Shahnan-Shah
Attorney Docket Number	CSI 130

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Appeal Brief; Ten (10) references

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Pabst Patent Group LLP		
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Printed name	Patrea L. Pabst		
Date	January 8, 2007	Reg. No.	31,284

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FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 0.00

Complete if Known	
Application Number	10/613,975
Filing Date	July 3, 2003
First Named Inventor	Donald L. Wise
Examiner Name	Khatol Shahnan-Shah
Art Unit	1645
Attorney Docket No.	CSI 130

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	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)	Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
_____ - 21 or HP =	0 x	_____	= _____	_____	_____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 3 or HP =	0 x	_____	= _____

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3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
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4. OTHER FEE(S)

Fees Paid ($)

Non-English Specification, $130 fee (no small entity discount) _____

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SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 31,284	Telephone (404) 879-2151
Name (Print/Type)	Patrea L. Pabst		Date January 8, 2007

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Donald L. Wise, Debra J. Trantolo, David D. Hile, and Stephen A. Doherty		
Serial No.:	10/613,975	Art Unit:	1645
Filed:	July 3, 2003	Examiner:	Khatol Shahnan-Shah
For:	*VACCINES TO INDUCE MUCOSAL IMMUNITY*		

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Commissioner for Patents
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APPEAL BRIEF

Sir:

Appellants have requested reinstatement of the Appeal filed February 22, 2006. With only very minor differences, the same issues are present in the office action rejecting claims 1 and 3-11 mailed August 7, 2006, in the above-identified patent application. A Notice of Appeal was re-filed on November 11, 2006. The Commissioner was originally authorized to charge the fee for filing the Appeal Brief for a large entity, to Deposit Account No. 50-3129, February 22, 2006, so no additional fee should be required. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

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(1) REAL PARTY IN INTEREST

The real party in interest of this application is Depuy Mitek, a Johnson & Johnson company.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 1 and 3-11 are pending and on appeal. Claims 2 and 12-21 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

It appears the examiner is confused with regard to the status of claim 2. As was corrected noted in the Office Action mailed November 3, 2004, claim 2 was cancelled and claim 3 was amended. See also the Amendment mailed August 10, 2004, page 2. It may be that the record is in error.

(4) STATUS OF AMENDMENTS

The claims were last amended in an amendment filed on January 4, 2007, in response to the office action mailed on August 7, 2006. In a telephone call with the examiner on January 8, 2007, the examiner indicated that this amendment would be entered.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the

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pathogen encapsulated in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof. Support for claim 1 can be found in the specification at least at page 8, lines 5-6, 16-18 and 20; at page 11, lines 1-2; page 20, lines 10-11; page 10, lines 26-27; page 25, lines 17-20 and claim 1 as originally filed. As defined by claim 3 the composition comprises a mucoadhesive polymer coating (see at least page 25, lines 17-20). As defined by claim 4, the composition comprises an enteric outer coating or capsule (see at least page 20, lines 28-31).

As defined by claim 5, the composition has a particulate diameter of less than five microns (see at least page 8, lines 12-13). Claim 8 defines the polymer as a low molecular weight poly(D,L-lactide-co-glycolide) (see at least page 8, lines 3-5).

Claim 9 defines the pathogens as selected from the group consisting of *Plasmodium falciparum, Francisella tularensis, Bacillus anthracis*, and *Helicobacter pylori* (see page 7, lines 9-12). Claim 10 defines the composition as also containing an adjuvant (see at least page 23, lines 9-10). Claim 11 defines the antigen as expressed or released for a period of weeks to months (see at least page 8, lines 13-16).

As defined by claim 6 the composition is formed by lyophilizing a solution of a biodegradable polymer to form an open-celled polymeric foam of approximately 95% void volume (see at least page 8, lines 5-6), impregnating the foam with an aqueous solution of the nucleic acid (see at least page 8, lines 6-7, lyophilizing the foam to remove the water (see at least page 8, lines 7-8, and extruding the resulting matrix at ultrahigh pressures (see at least page 8, line 8). As defined by claim 7, the method also contains the step of cryogenically grinding the

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matrix to an average particle size of fifteen microns in diameter; and sieving to isolate particles less than five microns in diameter (see at least page 8, lines 10-13).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1 and 3-11 are enabled as required by 35 U.S.C. § 112, first paragraph.

(2) whether claims 1 and 3-11satisfy the written description requirement as required by 35 U.S.C. § 112, first paragraph.

(3) whether claim 9 id definite as required by 35 U.S.C. § 112, second paragraph.

(4) whether claims 1, 3-5 and 8-11 are anticipated by O'Hogen. *J. Pharm. Pharmacol.*, 50(1):1-10 (1998) ("O'Hogan")

(5) whether claims 1, 3-5, and 8 are anticipated by Perez, et al., J. *Control Release*, 75:211-224 (2001) ("Perez").

(7) ARGUMENT

(A) The Invention

Mucous membranes are the primary routes of entry for a large number and wide variety of disease carrying agents. Many pathogens enter and replicate at the mucosal surface before causing systemic infection. The mucosal immune system can be stimulated by oral administration. However, the induction of mucosal immunity has been shown to depend on a number of variables including the delivery system. Local administration of antigens usually requires large amounts of antigen to produce a response (see at least page 9). At stated at page 9,

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of the specification, delivery of antigen is key to developing an immune response and that under-stimulation may fail to prime the immune system. The present application relates to the development of effective and long-lasting vaccines, especially vaccines incorporating nucleic acid encoding antigen, such as plasmid DNA, by encapsulating the DNA within a mucoadhesive controlled release particulate formulation.

As discussed at least at page 17, administration of naked DNA leaves the vaccine vulnerable to attack by enzymes that can reduce the half-life to minutes or hours. Chemical modification can increase the half life of the vaccines, but this may also increase systemic toxicity. Vaccines, including DNA vaccines, have been widely available for a long time. However, no one has put them into into a mucoadhesive controlled release particulate formulation, as claimed herein. As discussed at least at page 8, the mucoadhesive controlled release particulate formulation protects the antigen and stimulates and maintains the immune response to pathogens.

(B) Rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 1 and 3-11 were rejected as non-enabled.

The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under 35 U.S.C. § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at

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1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

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As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. See *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). There is no requirement for examples.

As the Board of Patent Appeals stating,

"Nevertheless, "[w]hen rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

Analysis

Claim 1 is enabled

The present application is directed to compositions which provide controlled release of DNA vaccines. The claims define encapsulating nucleic acid encoding an antigen eliciting an

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immune response to a pathogen in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof. DNA encoding antigen is encapsulated into a mucoadhesive controlled release particulate formulation to achieve sustained delivery of the vaccine and to maintain an immune response.

The specification clearly enables a skilled artisan to make and use the claimed vaccine formulatoin. The pathogens and antigens are known. The specification at least at page 11, lines 1-3 states that the antigen is a nuclei acid molecule encoding a protein that induces immunity. Suitable antigens are known and available from commercial, government and scientific sources (see the specification at least at page 11, lines 14-15). The claims are drawn to a new formulation providing a means for enhancing mucosal delivery of these nucleic acids encoding known antigens. The claims are drawn to an improved DNA vaccine formulation generally, not a specific vaccine. Appellants do not claim to have invented DNA vaccines, and indeed have provided much evidence to show that DNA vaccines are known. The specification and application instead are drawn to the advantages obtained using the polymeric carrier.

The best evidence against the examiner's rejection is the article cited by the Examiner in the Office Action mailed December 22, 2003, O'Hagan, *J. Pharm. Pharmacol.* 50:1-10 (1997) ("O'Hagan"), a copy of which is enclosed in the Appendix, **dated four years before the priority date of this application**. O'Hagan makes clear that even as of 1997, nucleic acid vaccines, while not being perfect and having some FDA issues, were effective and could be delivered using a polymeric carrier. Additional papers were enclosed with the Amendment and

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Response filed August 10, 2004 to show that DNA vaccines are considered to be enabled and vaccination with them does not require "undue experimentation". See Pachuk, et al. Curr Opin Mol Ther. 2(2):188-98 (April 2000); Barnes, et al. Curr Opin Mol Ther. 2000 Feb;2(1):87-93 (February 2000); and Watts and Kennedy Int. J. Parasitol. 29(8):1149-63 (1999) ("Watts"), copies of which are enclosed in the Appendix. The Examiner pointed to Pachuk, page 188 wherein is stated that "DNA vaccine technology is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans as rebuttal to Appellants use of Pachuck as evidence that DNA vaccines are enabled. Appellants respectfully draw the Examiners attention to the fact that Pachuk is not stating that research needs to be done for DNA vaccines to work, but to improve the efficiency with which they work, which means that they do work. Also, the Examiner quoted from Pachuk at page 195, which states "it is recognized that one of the major limitations to the success of DNA vaccines is its delivery. This in fact is the problem the present application seeks to solve (see the specification at least from page 9, line 26until page 10, line 31). Also quoted by the Examiner was the sentence in Pachuk stating that "it is unclear which cells are to be targeted for optimal eliciting of immune response" (referencing Pachuk, page 188). The specification discusses the cells to be targeted at least at page 10, lines 19-31.

The examiner has provided no evidence whatsoever that this method would not work; only unsupported allegation based on the belief that "the claims are very broad" (page 3, August 7, 2006, in a statement identical to the previous office action).

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Applying the *Wands* factors, it is clear from the amount of direction and guidance in the specification that sufficient detail is provided to one of ordinary skill in the art to make and use the claimed composition.

The quantity of experimentation, the state of the prior art, the relative skill of those in the art, and the predictability of the art

The skill of one in the art is high. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The genetic manipulation of plasmid DNA is **highly** routine in the art. As described in Watts, plasmid vectors can be rapidly constructed and easily tested. All that is required is the DNA sequence of the antigen. Watts and the specification on pages 4-6 and pages 11-17, for example, disclose a number of DNA vaccines for bacterial, viral, and parasitic pathogens suitable for use in the claimed formulation of the present application. Therefore, the creation of numerous, different plasmids encoding antigens from a variety of pathogens would be routine experimentation for one of ordinary skill in the art. In addition, the skill of one in the art with respect to incorporation of active agents into polymers is also high (for example, see page 21, last paragraph). There is also predictability in the art with respect to delivery of vaccines by polymeric particles (for example, see page 20, lines 2-18).

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The amount of direction and guidance presented, the presence of working examples, the nature of the invention.

The claims define compositions wherein nucleic acid encoding an antigen is encapsulated in a mucoadhesive controlled release particulate formulation. The specification describes the use of these vaccine compositions to induce an immune response against pathogens such as malaria, anthrax, tularemia, and *H. pylori*. The specification at least at pages 4-6 and pages 11-17, discloses a number of DNA vaccines for bacterial, viral, and parasitic pathogens suitable for use in the claimed formulation of the present application. The specification discloses the encapsulation of DNA in a biodegradable polymer to achieve slow release into the system at least at pages 17-20. Finally, the specification provides ***in vivo*** data in BALB/c mice immunized with vaccine/PLGA (recited in claim 8) particles, PLGA-alone, or a control oligodeoxynucleotide/PLGA particles verifying protective immunity only in mice immunized with the vaccine/PLGA particles (see pages 32-33).

Claim 3 is enabled

Mucoadhesives are known in the art, and the specification discloses the addition of a mucoadhesive at least at pages 21-23. It would be routine for a skilled artisan to make a vaccine as defined by claim 3, which comprises a mucoadhesive, as described by the specification. In fact, the specification provides as an example, the use of gelatin as a mucoadhesive and the improved mucoadhesion observed with particles with gelatin as an added component (see the specification from page 22, line 1page 23, line 2.

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The examiner has provided no basis for alleging one would not know how to make a mucoadhesive formulation. Therefore, claim 3 is enabled.

Claim 4 is enabled

Enteric coatings are routinely used in the pharmaceutical art, can be purchased commercially, and the specification at least at page 23, lines 9-14 provides an example of an enteric coating. It would therefore be routine for a skilled artisan to make a vaccine as defined by claim 1 including an enteric outer coating or capsule as required by claim 4. Therefore, claim 4 is enabled.

Claims 5-8

Claim 5 defines a vaccine composition for inducing an immune response to a pathogen using a nucleic acid encoding an antigen eliciting an immune response to the pathogen, wherein the nucleic acid is encapsulated in a mucoadhesive controlled release particulate formulation. The examiner has provided no basis for the allegation that one would not know how to make a particulate formulation as claimed, and indeed later asserts that the prior art discloses just such a formulation. Claim 5 is enabled.

As defined by claims 6 and 7, the composition can be formed by a method that contains the following steps: (1) lyophilizing a solution of a biodegradable polymer to form an open-celled polymeric foam of approximately 95% void volume, (2) impregnating the foam with an aqueous solution of the nucleic acid, (3) lyophilizing the foam to remove the water, and (4) extruding the resulting matrix at ultrahigh pressures as defined by claim 6 (disclosed least at

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pages 27-28). Again, the examiner has provided no basis for rejecting this claim other than the allegation that because the claims are "very broad" they must not be enabled.

The specification discloses administration of the vaccines at least at page 32. The specification at least at page 26 describes appropriate size ranges for the particles as defined by claims 5 and 8. Methods for encapsulating nucleic acids into the polymeric foam are disclosed in the specification on page 19. Therefore the specification not only describes how to make and use the claimed formulation, but demonstrates that appellants have actually made and used the formulation.

Claim 8 adds the further limitation that the polymer in the formulation is a low molecular weight poly(D,L-lactide-co-glycolide) ("PLGA"). These polymers are available from a number of commercial suppliers. Claim 8 is enabled for the same reasons as claims 1 and 6-7.

Claim 9 is enabled

The specification from page 1, line 23 to page 6, line 7 discusses in detail malaria, tularemia, and anthrax, diseases which are caused by *Plasmodium falciparum*, *Francisella tularensis*, and *Bacillus anthracis*, respectively. Antigens to these pathogens are known in the art (see the specification from page 11 to page 17, discussing antigens to the four pathogens listed in claim 9. It would be routine for a skilled artisan to make a nuclei acid molecule encoding antigens to these pathogens and encapsulate them in a mucoadhesive controlled release formulation, based on the teachings in the specification, for the manufacture of a vaccine formulation for inducing an immune response to the pathogens listed in claim 9. Therefore, claim 9 is enabled.

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Claim 10 is enabled

Adjuvants are known in the art, and the specification at least at page at page 11, lines 17-24 provides examples. It would therefore be routine for a skilled artisan to make a vaccine as defined by claim 1 including adjuvants as required by claim 10, as described in the specification, for the reasons discussed above. Therefore, claim 10 is enabled.

Claim 11 is enabled

Methods for measuring DNA release are known in the art, and are disclosed in the specification at least from page 29, line 18, to page 31, line 28. The specification at least from page 23, line 19, to page 24, line 16, provides an example showing recovery of DNA from PLGA matrices throughout a 6 week incubation period. The examiner has provided no reason why one skilled in the art would not be able to measure DNA release, nor that the formulation of claim 1 would release DNA. Therefore, claim 11 is enabled.

Conclusion

The claims are drawn to vaccine compositions incorporating nucleic acid encoding antigen, such as plasmid DNA, made by encapsulating the DNA within a mucoadhesive controlled release particulate formulation. The standard for enablement is whether one skilled in the art would be able to make a vaccine composition as claimed. The prior art and specification teach the use of DNA in the production of vaccines against a vast array of diseases. One could routinely substitute these DNA sequences into the vaccine compositions as described in the specification to make a composition to induce an immune response. Appellants are not claiming any unique DNA, but DNA encoding antigens that are present in pathogens when incorporated

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into a mucoadhesive controlled release particulate formulation. The application clearly provides support for such a formulation, and provides actual working examples.

Claim 9 is not drawn to a broad range of pathogens, but to four specific pathogens. It appears in generalizing the rejection to all of the independent claims that the examiner has failed to individually examine the dependent claims, as required.

(C) Rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 1 and 3-11were rejected under 35 U.S.C §112 first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

The Legal Standard

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I). All that is required is that the specification provides sufficient description to **reasonably** convey to those skilled in the art that, as of the filing date sought, that the inventor was in possession of the claimed invention. *Union Oil of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000); *Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed

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invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. M.P.E.P. § 2163(I), citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 66, 48 USPQ2d 1641, 1646 (1998).

In a recent decision by the Board of Patent Appeals and Interferences, the Board warned that it is an improper analysis to determine that the claims are directed to an invention which is broader than that which is described in the specification since the written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-64. Thus the Board re-emphasized that the specification need not always spell out every detail; only enough "to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *LizardTech Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-34, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

Analysis

The examiner's rejection appears to be based solely on the conclusory statement that the claims are "very broad" and completely fails to address each of the dependent claims. The rejections simply states that "The specification and the claims do not indicate what

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distinguishing attributes are shared by the members of the genus (Pathogens)" Page 7, August 7, 2006 Office Action.

This is wrong. Appellants have repeatedly, and consistently, explained that the feature shared by the "Pathogens" are that they are pathogens and that they all have DNA that encodes antigenic proteins that can be put into the claimed composition for use as a vaccine. Nothing more is needed. Although there is only one example, the written description requirement has never been limited to examples of actual reduction to practice, but on the written description. The written description clearly and unequivocally discloses a large number of antigens that can be incorporated into the composition for use as vaccines.

Claim 1

It is clear form the description in the specification that the Applicants were in possession of the claimed subject matter. The claims define a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume or particles thereof.

Claims 1, 3-11

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. (See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406). A "representative number of species" means that the species which are adequately described are representative of the entire genus. There may be situations where even

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one species can adequately supports a genus (see, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27; In re *Herschler*, 591 F.2d at 1214, 211 USPQ at 326-27). The specification teaches more than one species for the nucleic acids recited in the claims. However, antigens to pathogens are known in the art. See Partidos, et al, *J. Immunol.* 195:135-38 (1996), Pertmer, et al., *Vaccine*, 13(15):1427-30 (1995), *Singh, et al., Pharm. Res*, 8(7):958-61 (1991), Smith, et al., *Oral Microbiol. Immunol.*, 15:124-30 (2000), and Thomasin, et al., *J. Control Rel.* 41:131-145 (1996) (a copy of each is attached to the evidence appendix), for an example of measles virus antigen, nucleic acid encoding an influenza virus antigen, *Diphtheria* toxoid, *Streptococcus sobrinus* antigen, and a tetanus toxoid respectively. The compositions employ nucleic acids of antigens already known in the art, formulating them in a manner that enhances their delivery to the mucosa. The specification refers to, and the literature provided by appellants further demonstrates, that adjuvant can be provided with the antigen – and, indeed, the polymer can be the adjuvant (pages 20-21), and that antigen can be expressed or released for a period of weeks to months. See page 18 and page 24, lines 8-14, showing actual reduction to practice of the claimed subject matter. Accordingly, claims 1, 3-8, 10 and 11 clearly comply with the written description requirement.

Claim 9

Claim 9 is limited to four specific pathogens: malaria, tularemia, anthrax and *Helicobacter pylori*. As discussed above, the present application relates to the development of effective and long-lasting vaccines, especially vaccines incorporating nucleic acid encoding antigen, such as plasmid DNA, by encapsulating the DNA within a mucoadhesive controlled

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release particulate formulations comprising an open-celled polymeric foam of approximately 95% void volume. The specification from page 11, line 13, until page 17, line 3, describes suitable antigens, which are known in the art, and are available from commercial, government and scientific sources (see the specification at least at page 11, lines 14-15). Moreover, the specification provides examples of antigens from *P. falciparum, F. tularensis, B. anthracis, H. pylori*, defined specifically by claim 9. Accordingly, claim 9 clearly complies with the written description requirement.

Claims 3-8

As affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art. The specification on page 19, describes how to encapsulate the nucleic acid encoding vaccine in a particulate formulation. Bioadhesives required by claim 3 are known in the art, and the specification at least from page 22, line 1 until page 23 line 18 describes how to incorporate a bioadhesive in the polymeric foam. The specification at least at page 25 and from page 27, line 25, until page 28, line 12 describes how to prepare and open-celled polymeric foam of approximately 95% void volume, and how to load the polymer with plasmid containing the nucleic acid of choice. DNA release is described from page 23 line 19, until page 24, line 14. Enteric coatings (required by claim 4) are routinely used in the art, and the specification at least at page 23, lines 9-14 provides an example of an enteric coating. Adjuvants (required by claim 10), which are known in the art, are described in the specification at least at page 11, lines 17-

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24). It is very clear that Appellants were in possession of the claimed invention, therefore, claims 1, and 3-11 satisfy the written description requirement.

Claims 6 and 7

Claims 6 and 7 are drawn to compositions made by methods of making a foam with a high void volume (claim 6) and in particulate form (claim 7). These are fully described in the specification at pages 25-28, and show actual reduction to practice. Accordingly, claims 6 and 7 are fully enabled.

(D) Rejections under 35 U.S.C. § 112, second paragraph

Claim 9 was rejected under 35 U.S.C. §112 second paragraph as allegedly reciting improper Markush language. The amendment and response filed on January 5, 2006moots this rejection, amending claim 9 to recite the pathogens that cause these diseases.

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(E) Rejections under 35 U.S.C. § 102(b)

Claims 1 and 3-11 are novel over O'Hagan and Perez.

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and **every** element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

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"A claim limitation is inherent in the prior art if it is necessarily present in the prior art, not merely probably or possibly present. "*Akamai Technologies, Inc. v. Cable & Wireless Internet Services, Inc.* , 344 F.3d 1186, 1192, 68 USPQ2d 1186 (Fed. Cir. 2003)".

O'Hagan

O'Hagan is a review article discussing the advances in vaccine adjuvants for systemic and mucosal administration ***prior to 1997***. It should be noted that O'Hagen is cited above by Appellants to support enablement of their claims, since O'Hagan describes vaccines, including vaccines made by recombinant DNA technology and nucleic acid based vaccine, as being known and effective no later than 1997, five years before the priority date of this application.

O'Hagan discloses the use of biodegradable polymers as vaccine adjuvants, in particular, the encapsulation of protein antigens into poly(lactide-co-glycolides) microparticles and the use of emulsions formed of materials such as mineral oil, and those which are advantageous for mucosal administration.

O'Hagan does not disclose an important limitation of all of claims 1 and 3-11: an open-celled polymeric foam of approximately 95% void volume, or particles thereof.

The examiner's conclusory "its inherent" is not only unsupported in fact, but legally incorrect. Inherency requires more than a mere possibility. The Federal Circuit has clearly set forth the standard for evaluating inherency in *In re Robertson*, 49 U.S.P.Q. 1949 (Fed. Cir. 1999). The court held that a claim element is not "inherent" in the disclosure of a prior art reference unless extrinsic evidence clearly shows that missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of

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ordinary skill in the art. "Inherency, however, may not be established by mere probabilities or possibilities" (49 U.S.P.Q. at 1950-51). Nothing the examiner has cited makes it likely, much less necessarily present, that O'Hagan discloses a foam with a 95% void volume. Accordingly, O'Hagan does not disclose the claimed subject matter.

Perez

Perez discloses the production and characterization of poly(lactic acid)-poly(ethylene) nanoparticles containing a high loading of plasmid DNA in a free form or co-encapsulated with either poly(vinyl alcohol) or poly(vinylpyrrolidine).

The same arguments apply equally to Perez. Nothing the examiner has cited makes it likely, much less necessarily present, that Perez discloses a foam with a 95% void volume. Accordingly, O'Hagan does not disclose the claimed subject matter

Claims 1, 3-11 are novel over O'Hagan and Perez

None of O'Hagan or Perez discloses the claimed vaccine composition. The claims require that the nucleic acid be encapsulated in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume or particles thereof. O'Hagan does not disclose encapsulating nucleic acid vaccines in a polymeric foam material, nor any method for making a foam with a high void volume. While O'Hagan states that delivery of a vaccine composition by mucosal administration would be "ideal" (Table 1, p. 2), the reference does not teach or suggest enhancing antigenicity by increasing mucoadhesion. Perez discloses that interesting results were found following oral administration of mucoadhesive particles such as polyanhydride microspheres. Perez does not disclose an open-

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celled foam. The Examiner has alleged that the characteristic of "an open-celled polymeric foam with a 95% void volume" would be an inherent property of a microparticle formulated for mucosal delivery.

According to the MPEP §2112 (IV), "In relying upon the theory of inherency, the examiner **must** provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)".

Hsu, et al., *J. Biomed. Mat. Res.*, 35:107-116 (1997) ("Hsu", a copy of which is attached), describes open-celled foams, their method of manufacture and characteristics (page 110, left column). It is readily apparent from Hsu that the nanoparticles disclosed in Perez (See figure 2 of Perez) do not have the claimed structure. The only basis for the rejection is that Perez discloses a polymer composition and appellants claim a polymer composition. The structures in which the nucleic acid is encapsulated are very different. The structures are different, the functions are different, and the methods of manufacture and use are different. "In order for a claim to be inherent in the prior art it is not sufficient that a person following the disclosure sometimes obtains the result set forth in the claim, it **must invariably happen.**" The Examiner has provided no evidence showing that the method for producing the nanoparticles disclosed in Perez sometimes results in a polymeric foam, certainly not that it invariably leads to the formation of a polymeric foam as required for the determination of inherency. The Examiner has provided no reasoning whatsoever for this conclusion of inherency. Neither O'Hagan nor Perez

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recite all of the limitations of the claims, therefore, claims 1 and 3-11 are novel over O'Hagan and Perez.

Claim 3 is novel over O'Hagan and Perez

Claim 3 requires that the composition of claim 1 further comprise a mucoadhesive polymer coating. As previously discussed, O'Hagan does not disclose the encapsulation of DNA in a mucoadhesive controlled release particulate formulation, nor that the composition further comprise a mucoadhesive. Perez does not disclose a formulation comprising an open-celled foam for encapsulating nucleic acid, which further comprises a mucoadhesive polymer coating. Therefore, claim 3 is novel over O'Hagan and Perez.

Claim 4 is novel over O'Hagan and Perez

Claim 4 requires that the composition of claim 1 further comprise an enteric outer coating or capsule. Neither of O'Hagan nor Perez disclose a composition for inducing an immune response to a pathogen, that comprises an open-celled polymeric foam of approximately 95% void volume or particles thereof, and further comprises an enteric outer coating or capsule as recited in claim 4. Therefore, claim 4 is novel over O'Hagan and Perez.

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Claim 9 is novel over O'Hagan and Perez

Claim 9 recites all of the limitations of claim 1 and requires that the pathogen be *Plasmodium falciparum, Francisella tularensis, Bacillus anthracis* and *Helicobacter pylori* None of O'Hagan or Perez disclose a composition for inducing an immune response to any of the pathogens listed in claim 9, using a composition comprising an open-celled polymeric foam of approximately 95% void volume. Therefore, claim 9 is novel over O'Hagan and Perez.

Claim 10 is novel over O'Hagan and Perez

Neither O'Hagan nor Perez disclose an adjuvant. Therefore claim 10 is novel over O'Hagan and Perez.

Claim 11

Neither O'Hagan nor Perez disclose release of antigen over a period of weeks to months from an open celled foam. Accordingly, claim 11 is novel over O'Hagan and Perez.

(8) Conclusion

Claims 1 and 3-11 are enabled and in compliance with the requirements of 35 U.S.C. 112. One of skilled in the art would be able to make and use the claimed compositions from the description Appellants have provided and Appellants have demonstrated they were in possession of the claimed subject matter at the time this application was filed.

Claim 9 as amended is definite but would be in compliance with 35 U.S.C. 112 even if not amended since the standard is whether one skilled in the art would understand the meaning of the claim, not whether it could be stated more articulately.

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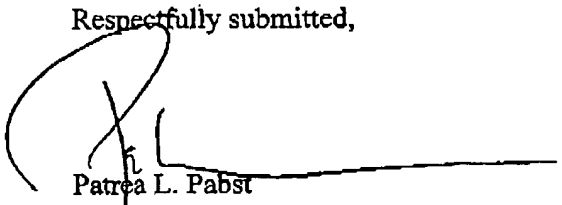
Claims 1 and 3-11 are novel over the cited art, O'Hagan and Perez, since neither O'Hagan nor Perez disclose each and every claimed limitation. Moreover, even if the references in combination disclosed each claimed limitation, there is no motivation to modify and combine as appellants have done, with a reasonable expectation of success in long term release of antigen.

Accordingly, allowance of claims 1, and 3-11 is earnestly solicited.

Respectfully submitted,



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Claims Appendix: Claims On Appeal

1. A vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof.

3. The composition of claim 1 further comprising a mucoadhesive polymer coating.

4. The composition of claim 1 further comprising an enteric outer coating or capsule.

5. The composition of claim 1 having a particulate diameter of less than five microns.

6. The composition of claim 1 formed by

lyophilizing a solution of a biodegradable polymer to form an open-celled polymeric foam of approximately 95% void volume,

impregnating the foam with an aqueous solution of the nucleic acid,

lyophilizing the foam to remove the water, and

extruding the resulting matrix at ultrahigh pressures.

7. The composition of claim 1 wherein the method further comprises cryogenically grinding the matrix to an average particle size of fifteen microns in diameter; and

sieving to isolate particles less than five microns in diameter.

8. The composition of claim 1 wherein the polymer is a low molecular weight poly(D,L-lactide-co-glycolide).

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9. The composition of claim 1 wherein the pathogen is selected from the group consisting of *Plasmodium falciparum*, *Francisella tularensis* , *Bacillus anthracis*, and *Helicobacter pylori* .

10. The composition of claim 1 further comprising providing an adjuvant with the antigen.

11. The composition of claim 1 wherein the antigen is expressed or released for a period of weeks to months.

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Evidence Appendix

Evidence submitted with the Information Disclosure statement filed on October 28, 2003

Hsu, et al., *J. Biomed. Mat. Res.*, 35:107-116 (1997)

Partidos, et al, *J. Immunol.* 195:135-38 (1996)

Pertmer, et al., *Vaccine*, 13(15):1427-30 (1995)

Singh, *et al., Pharm. Res*, 8(7):958-61 (1991)

Smith, et al., *Oral Microbiol. Immunol.*, 15:124-30 (2000)

Thomasin, et al., *J. Control Rel.* 41:131-145 (1996)

Evidence cited by the Examiner in office action dated December 22, 2003

O'Hagan, *J. Pharm. Pharmacol.*, 50:1-10 (1997).

Evidence submitted with Amendment and Response filed August 10, 2004

Pachuk, et al. *Curr Opin Mol Ther.*, 2(2):188-98 (April 2000).

Barnes, et al. *Curr Opin Mol Ther.*, 2000 Feb;2(1):87-93 (February 2000).

Watts and Kennedy, *Int. J. Parasitol.*, 29(8):1149-63 (1999).

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Related Proceedings Appendix

None

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